$Beta_2$ Adrenergic Agents – Long-Acting Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Reversible Bronchospasm		Prevention of Exercise-Induced Broncho-constriction	Chronic Obstructive Pulmonary Disease (COPD)	Age of Use (years)
		Prevention and Treatment	Relief			
Long-Acting Inhalation Agents						
arformoterol inhalation solution (Brovana®)[1]	Sunovion	--	--	--	X	≥18
formoterol inhalation powder in capsules (Foradil® Aerolizer®)[2]	Merck Sharp & Dohme	X	--	X	X	≥5
formoterol inhalation solution (Perforomist®)[3]	Dey	--	--	--	X	≥18
indacaterol inhalation powder (Arcapta™ Neohaler™)[4]	Novartis	--	--	--	X	≥18
olodaterol inhalation spray (Striverdi® Respimat®)[5]	Boehringer Ingelheim	--	--	--	X	≥18
salmeterol DPI (Serevent® Diskus)[6]	GlaxoSmithKline	X	--	X	X	≥4

DPI=dry powder inhaler

COPD=Chronic Obstructive Pulmonary Disease

Arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi) are not indicated for the treatment of acute deteriorations of chronic obstructive pulmonary disease (COPD) or the management of asthma.

The dry powder inhalation (DPI) form of formoterol (Foradil® Certihaler®) approved in 2006 is not currently being marketed in the United States (U.S.).

OVERVIEW

Beta$_2$-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of COPD.

Asthma

The mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) and long-acting beta$_2$-agonists (LABAs) as controller medications.[7] These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists (SABAs) for quick relief. LABAs are not to be used as monotherapy for controlling asthma. While the corticosteroid reduces inflammation, the long-acting beta$_2$-agonist acts principally to dilate the airways by relaxing airway smooth muscle. However, according to the 2015 Global Initiative for Asthma (GINA) update to the Global Strategy for the Diagnosis and Management of Asthma in Children five years and younger, the effect of a LABA or combination LABA/inhaled glucocorticoid has not been adequately studied in this patient population.[8] Therefore, LABAs cannot be recommended in this age group.

The 2007 guidelines from the National Heart Lung and Blood Institute (NHLBI) recommend that, for patients over age five years with moderate persistent asthma or asthma not controlled by low-dose corticosteroids, consideration be given for use of a combination of ICS and LABAs or for increasing the dose of ICS.[9] For patients with severe persistent asthma, a combination of a LABA and an ICS is recommended. For EIB, LABAs may be used for prevention; however, it is noted that frequent or chronic use may disguise poorly controlled persistent asthma.

In November 2007, the National Asthma Education and Prevention Panel (NAEPP) released a summary of the third report of the Expert Panel (EPR-3) emphasizing the importance of asthma control and identifying asthma severity as the intrinsic intensity of the disease process.[10] The recommendation from EPR-3 is to assess severity to initiate therapy and assess control to adjust therapy in patients as young as five years of age.

The 2015 Global Initiative for Asthma (GINA) guidelines state that the assessment of asthma control should include control of the clinical manifestations and control of the expected future risk to the patient, such as exacerbations, accelerated decline in lung function, and side-effects of treatment.[11] GINA classifies asthma in terms of three levels of control, controlled, partly controlled, or uncontrolled, and provides a five-step treatment approach which offers flexibility to step up treatment if control is lost or to step down treatment when asthma is controlled. In each step, reliever medication should be provided for quick relief, as needed. LABAs are included as options in steps 3 and 4, in combination with ICS. GINA advises that LABAs should not be used as monotherapy in asthma as these medications do not appear to influence airway inflammation in asthma. These guidelines state that LABAs are most effective when combined with ICS and that combination therapy is the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma. Addition of LABAs to a daily regimen of ICS improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of SABAs, reduces the number of exacerbations, and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of ICS than ICS given alone. Increased use of reliever medications is a warning of deterioration in asthma control that indicates a need to reassess treatment.

COPD

Bronchodilator medications are central to the symptomatic management of COPD.[12,13,14,15] They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. [16] They are given either on an as-needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Regular bronchodilation with these drugs does not modify the decline of lung function in mild COPD or the prognosis of the disease.[17] The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or in combination. While SABAs can be used on an as-needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.[18]

The 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) state that beta$_2$-agonist bronchodilators are among the principal treatments for symptomatic management of COPD.[19] Previous guidelines list four stages of spirometric classification of COPD severity: stage 1 – mild; stage 2 – moderate; stage 3 – severe; and stage 4 – very severe. While forced expiratory volume in one second (FEV_1) was used previously to qualify disease severity, the revised guidelines state that FEV_1 is an

unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment. While the classification system remains the same, the terminology has shifted from "Stages" to "Grades" for population-based risk classification. Now, the grading system is as follows: GOLD 1 – Mild; GOLD 2 – Moderate; GOLD 3 – Severe; and GOLD 4 – Very Severe. It uses the fixed ratio, post bronchodilator FEV_1/forced vital capacity (FVC) < 0.7 to define airflow limitation. It is recognized that the use of the fixed ratio may lead to more frequent diagnoses of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows, and may lead to under-diagnosis in adults younger than 45 years. Another classification system also exists that is a combined classification based on the GOLD grade in conjunction with a symptomatic assessment and a patient's exacerbation history. The classification system involves assessing symptoms using the modified British Medical Research Council (mMRC) or COPD Assessment Test (CAT) to determine if the patient has fewer symptoms (mMRC grade 0-1 or CAT < 10) or more symptoms (mMRC grade ≥ 2 or CAT ≥ 10). Next, the risk of exacerbations is assessed using either the GOLD population-based risk assessment or the number of exacerbations within the last 12 months (≤ 1 indicates low risk while ≥ 2 indicates high risk). If the two risk assessments differ, the higher risk assessment should be used. The classification system is divided into four groups:

Group A: Low Risk, Less Symptoms – Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year AND mMRC grade 0-1 or CAT < 10

Group B: Low Risk, More Symptoms – Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year AND mMRC grade ≥ 2 or CAT ≥ 10

Group C: High Risk, Low Symptoms – Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbation per year AND mMRC grade 0-1 or CAT < 10)

Group D: High Risk, More Symptoms – Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation) and/or ≥ 2 exacerbation per year AND mMRC grade ≥ 2 or CAT ≥ 10

The advantage of the combined approach is that it demonstrates the complexity of COPD better than the GOLD population-based risk classification system and facilitates individualized therapy. Short-acting bronchodilators are used as needed and are considered first-line treatment for patients in Group A. Long-acting bronchodilators are recommended in patients with more advanced disease, either alone or in combination with other agents depending on disease severity. For patients with repeat exacerbations, ICS may be added to the daily treatment regimen. In addition, the guidelines state that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. None of the existing medications for COPD have been shown conclusively to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations and hospitalizations, and improve health status and exercise tolerance.

Devices

In 2005, the American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.[20] The authors performed a systematic review of randomized controlled trials comparing the efficacy and adverse effects of treatment using nebulizers versus pressurized metered-dose inhalers (MDIs), with or without a spacer/holding chamber, versus dry powder inhalers (DPIs) as delivery systems for $beta_2$-agonists, anticholinergic agents, and corticosteroids in several

commonly encountered clinical settings and patient populations. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

In children five years of age and younger, the 2015 GINA update maintains that inhaled therapy constitutes the cornerstone of asthma treatment.[21] The preferred delivery system is a pressurized MDI with a valved spacer (with face mask for < 4 years and mouthpiece for most 4 to 5 year olds). Since the dose may vary considerably from one spacer device to another, a spacer that has documented efficacy in young children is recommended. Nebulizers, the only viable alternative delivery system in children, should be reserved for the minority of children who cannot be taught effective use of a spacer device. The Neohaler, a dry powder inhaler device, is used exclusively with indacaterol (Arcapta).

PHARMACOLOGY[22,23,24,25,26,27]

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. $Beta_2$-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.[28,29]

Although there are both $beta_1$ and $beta_2$ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of $beta_2$ specific agonists is preferred in the treatment of bronchospasm. To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

PHARMACOKINETICS[30,31,32,33,34,35]

Drug	Relative $ß_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Long Acting Inhalation Agents			
arformoterol inhalation solution (Brovana)	$ß_2$ >>> $ß_1$	7-20	12
formoterol inhalation powder in capsules (Foradil Aerolizer)	$ß_2$ >>> $ß_1$	5-15	12
formoterol inhalation solution (Perforomist)	$ß_2$ >>> $ß_1$	11-13	12
indacaterol inhalation powder (Arcapta Neohaler)	$ß_2$ >>> $ß_1$	15	40 - 56
olodaterol inhalation spray (Striverdi Respimat)	$ß_2$ >>> $ß_1$	5-20	24
salmeterol DPI (Serevent Diskus)	$ß_2$ >>> $ß_1$	30-48	12

CONTRAINDICATIONS/WARNINGS[36,37,38,39,40,41]

In 2003, the Food and Drug Administration (FDA) updated the safety information for products containing salmeterol (Serevent, Advair). As a result, labeling for these products contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in the large, placebo-controlled Salmeterol Multicenter Asthma Research Trial (SMART). In the prematurely stopped study, only the single component agent, salmeterol, was administered. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African Americans. The FDA did indicate that the benefits of salmeterol in patients with COPD or asthma outweigh the risks.[42]

In 2006, the FDA requested that manufacturers of the long-acting beta$_2$-agonists (LABAs), salmeterol (Serevent, Advair) and formoterol (Foradil), update their product labeling to alert health care professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur. LABA-containing products that entered the market since 2006 also have the same warnings in the labeling.

LABAs should not be initiated in patients who are acutely deteriorating with COPD or for acute symptoms; a short-acting beta-agonist bronchodilator should be used for acute symptoms. LABAs should be used with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or with sensitivity to sympathomimetic drugs.

In 2010, the FDA issued new recommendations on the safe use of LABAs in the treatment of asthma.[43] These recommendations include contraindication of use of LABAs without the use of an asthma controller medication, such as an inhaled corticosteroid (ICS). Single ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone. LABAs should only be used long-term in patients whose asthma is not adequately controlled on asthma controller medications. LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication. Pediatric and adolescent patients who require the addition of LABAs to an ICS should use a combination product containing both an ICS and a LABA to ensure compliance with both medications.

Beta-adrenergic agonists can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, or symptoms, and should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Salmeterol (Serevent) is contraindicated in patients with severe hypersensitivity to milk proteins.

Arformoterol (Brovana) is contraindicated in patients with a known hypersensitivity to arformoterol, racemic formoterol (Foradil), or any of its components.

Indacaterol (Arcapta Neohaler) and olodaterol (Striverdi Respimat), like other LABAs, are contraindicated in patients with asthma without use of a long-term asthma control medication. Indacaterol is not indicated for the treatment of asthma.

DRUG INTERACTIONS[44,45,46,47,48,49]

Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants

All long-acting beta$_2$-agonists (LABAs) should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because these agents may potentiate the action of adrenergic agonists on the cardiovascular system. Allow two weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of LABAs, but beta-blockers may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, such as prevention of myocardial re-infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

CYP3A4 Inhibitors

Co-administration of salmeterol and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, and telithromycin) may result in a significant increase in plasma salmeterol exposure. Due to the potential increased risk of cardiovascular adverse event, the concomitant use of salmeterol with these agents is not recommended.

ADVERSE EFFECTS[50,51,52,53,54,55]

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
Long Acting Inhalation Agents						
arformoterol inhalation solution (Brovana)	<2	reported	<2	<2	<2	< 2
formoterol inhalation solution (Perforomist)	nr	4.9/2.4 (2.6/1.8)	nr	nr	nr	nr
formoterol inhalation powder in capsules (Foradil Aerolizer)	reported	reported	reported	reported	reported	1.9 (0.4)
indacaterol inhalation powder (Arcapta Neohaler)	5.1	2.4	nr	nr	reported	nr
olodaterol inhalation spray (Striverdi Respimat)	nr	nr	nr	nr	nr	nr
salmeterol DPI (Serevent Diskus)	13 (9)	3 (3)	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses.

nr = not reported.

SPECIAL POPULATIONS[56,57,58,59,60,61]

Pediatrics

Formoterol (Foradil Aerolizer) has been studied in children ages five and older for the prevention and treatment of asthma and prevention of EIB; recommended dosage is the same as for older children. Salmeterol (Serevent) is indicated for the prevention and treatment of asthma and prevention of EIB in children as young as four years.

Safety and effectiveness of indacaterol (Arcapta), arformoterol (Brovana), formoterol (Perforomist), and olodaterol (Striverdi) have not been established in children.

Pregnancy

All agents in this category are Pregnancy Category C.

DOSAGES[62,63,64,65,66,67]

Drug	Usual Adult Dosage	Prevention of EIB	Usual Pediatric Dose	Availability
Long Acting Inhalation Agents				
arformoterol inhalation solution (Brovana)	15 mcg twice daily	--	--	15 mcg/2 mL inhalation solution
formoterol inhalation powder in capsules (Foradil Aerolizer)	1 inhalation every 12 hours	1 inhalation 15 minutes prior to exercise	Ages 5 years and up: 1 inhalation every 12 hours	12 mcg of inhalation powder per capsule
formoterol inhalation solution (Perforomist)	20 mcg every 12 hours	--	--	20 mcg/2 mL inhalation solution
indacaterol inhalation powder (Arcapta Neohaler)	75 mcg inhaled once daily using the Neohaler inhaler	--	--	75 mcg capsules in aluminum blister cards
olodaterol inhalation spray (Striverdi Respimat)	2 inhalations once daily	--	--	2.7 mcg per inhalation
salmeterol DPI (Serevent Diskus)	1 inhalation every 12 hours	1 inhalation 30 minutes before exercise; not to administer a second dose within 12 hours	Ages 4 years and up: 1 inhalation every 12 hours	50 mcg per inhalation

A FDA Public Health Advisory issued in March 2008 emphasized the correct use of formoterol (Foradil) capsules, which are to be used in the Aerolizer device. These capsules should not be swallowed.[68]

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

formoterol DPI inhalation powder (Foradil) versus salmeterol DPI (Serevent) versus terbutaline MDI (Brethine)

Twenty-five subjects with asthma and a history of EIB were enrolled in a double-blind, double-dummy, placebo-controlled, randomized, four-period crossover study.[69] Exercise challenge was performed after 12 days at 5, 30, or 60 minutes after inhalation of a single dose of formoterol dry powder inhaler (DPI) 12 mcg, salmeterol DPI 50 mcg, terbutaline metered-dose inhaler (MDI) 500 mcg, or placebo. Exercise-induced bronchoconstriction (EIB) did not differ significantly among the active treatments at 5, 30, or 60 minutes postdose. In contrast, the onset of bronchodilation was slower after salmeterol DPI compared to terbutaline MDI ($p<0.05$) and formoterol DPI ($p<0.05$), both of which showed a similar time course. At all time points between 5 and 60 minutes, formoterol DPI provided significantly greater bronchodilation than salmeterol DPI ($p<0.05$). Terbutaline MDI is not currently marketed in the United States.

COPD

arformoterol (Brovana) versus salmeterol (Serevent) MDI

A 12-week, double-blind, randomized, double-dummy, placebo- and active-controlled trial in the U.S. compared arformoterol and salmeterol in 717 patients with COPD.[70] Patients were randomized to arformoterol 15 mcg twice daily, 25 mcg twice daily, or 50 mcg daily via nebulizer, salmeterol 42 mcg twice daily via MDI, or placebo. Groups were similar at baseline and had a mean baseline forced expiratory volume in 1 second (FEV_1) of 1.2 L (41% predicted). Mean improvement in trough FEV_1 over 12 weeks was significantly greater with all three arformoterol doses (15 mcg twice daily, +16.9%; 25 mcg twice daily, +18.9%; 50 mcg daily, +14.9%) and for salmeterol (+17.4%) relative to placebo (+6%; $p<0.001$). There were significantly greater improvements in the mean percentage change in FEV_1 $AUC_{(0-12h)}$ from the predose value over 12 weeks (arformoterol 15 mcg twice daily, 12.7%; 25 mcg twice daily, 13.9%; 50 mcg daily, 18.9%; salmeterol, 9.8%) versus placebo (2.7%; $p\leq0.001$); all doses of arformoterol were statistically different from salmeterol for this endpoint ($p=0.024$). Adverse effects and COPD exacerbations (defined as worsening respiratory status requiring a change in medication or an unscheduled provider visit) were similar in frequency across groups, including placebo.

arformoterol (Brovana) versus salmeterol MDI (Serevent) versus placebo

Data were pooled from two, identical, 12-week, double-blind, randomized trials to determine the effect of nebulized arformoterol on airway function in adult patients with COPD.[71] Patients were randomized to one of the following treatment groups: arformoterol 15 mcg twice daily (n=147), 25 mcg twice daily (n=149), or 50 mcg daily (n=147); salmeterol 42 mcg twice daily via MDI (n=146); or placebo (n=150). Both arformoterol and salmeterol showed an improvement in trough FEV_1 over 12 weeks greater than placebo. The arformoterol groups showed the following improvements in trough FEV_1: 15 mcg (11.4%); 25 mcg (15.4%); and 50 mcg (10.9%), respectively. The salmeterol group had an 11.6% improvement in trough FEV_1. Also, after 12 weeks, 78 to 87% of arformoterol patients had at least a 10% increase in FEV_1 compared to 56% for the salmeterol and 44% for the placebo groups. The study was conducted and funded by the manufacturer of arformoterol.

albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent)

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 patients with COPD.[72] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and 5, 15, 30, 60, and 120 minutes after bronchodilator (albuterol MDI 200 mcg, formoterol DPI 12 mcg, salmeterol DPI 50 mcg, or oxitropium 200 mcg) or placebo administration. Oxitropium was used in this study, but it is not available in the U.S. The results indicated that, in patients with COPD with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration which correlated closely with the improvement of dyspnea sensation at rest. There were significantly greater improvements in the mean percentage change in FEV_1 and area under the curve (AUC) (0-12h) from the predose value over 12 weeks for all treatment groups (15 mcg, 12.7%; 25 mcg, 13.9%; 50 mcg, 18.9%; salmeterol, 9.8%) versus placebo (2.7%; p≤0.001). On average, formoterol DPI elicited the greatest increase in inspiratory capacity than the other bronchodilators used, though the difference was significant only with salmeterol DPI (p≤0.024).

formoterol inhalation powder (Foradil) versus salmeterol DPI (Serevent)

Researchers compared the effects of single doses of formoterol 12 and 24 mcg and salmeterol DPI 50 and 100 mcg in a randomized, double-blind, placebo-controlled, crossover study of 47 patients with moderate-to-severe COPD.[73] The primary efficacy parameter was the area under the curve of FEV_1 in the first hour after drug inhalation in the morning. The estimates of treatment difference in absolute terms (0.086 L; p=0.0044) and percentage change from predose baseline (7.8%; p=0.0021) were greater for formoterol than for salmeterol.

formoterol inhalation solution (Perforomist) versus formoterol inhalation powder (Foradil) versus placebo

A 12-week, randomized, double-blind, double-dummy study of 351 patient with COPD (mean FEV_1=1.3L, 44% predicted) were randomized to receive nebulized formoterol fumarate 20 mcg, formoterol inhalation powder 12 mcg, or placebo to determine the comparative efficacy and safety associated with nebulized therapy in COPD patients.[74] Efficacy was assessed with 12-hour pulmonary function tests, and quality of life was assessed before and after treatment with the St. George's Respiratory Questionnaire (SGRQ). At the 12-week endpoint, formoterol inhalation solution significantly increased FEV_1 versus placebo (p<0.0001). There was no evidence of tachyphylaxis since the FEV_1 AUC was maintained, and rescue albuterol use was reduced throughout treatment. The SGRQ assessment at week 12 demonstrated significant and clinically meaningful improvements in total, symptom, and impact scores when comparing formoterol inhalation solution to placebo (p=0.0067). No significant differences in efficacy were observed between the two active treatments. The safety profile was comparable between the formoterol inhalation solution and the formoterol inhalation powder.

indacaterol (Arcapta Neohaler) versus placebo

Six confirmatory, randomized, double-blinded, placebo- and active-controlled trials of indacaterol were conducted.[75] These six trials enrolled 5,474 patients with the clinical diagnosis of COPD, who were age 40 years or older, had a smoking history of at least 10 pack-years, had a post-bronchodilator FEV_1 less than 80% and at least 30% of the predicted normal value and a post-bronchodilator ratio of FEV_1 over forced vital capacity (FVC) of less than 70%. The primary efficacy endpoint was 24-hour, post-dose trough FEV_1 (defined as the average of two FEV_1 measurements taken after 23 hours 10 minutes and 23 hours and 45 minutes after the previous dose) after 12 weeks of treatment in all six trials. Other efficacy variables included other FEV_1 and FVC time points, rescue medication use, symptoms, and health-related quality of life measured using the SGRQ. In all six confirmatory COPD trials, all doses of indacaterol showed significantly greater 24-hour, post-dose trough FEV_1 compared to placebo at 12 weeks. Results of the trials which compared indacaterol at the dose of 75 mcg once daily to placebo were statistically significant in favor of indacaterol, with trough FEV_1 of 1.38 to 1.49 L compared to 1.26 to 1.35 L for placebo.

olodaterol (Striverdi) versus placebo

Eight confirmatory, randomized, double-blind, placebo-controlled trials were conducted in COPD patients taking olodaterol.[76] Patients (n=3,533) were 40 years of age or older, had a smoking history of at least 10 pack-years, had moderate to very severe pulmonary impairment, and had a post-bronchodilator FEV_1/FVC ratio of less than 70%. The primary efficacy endpoints for four trials were change from pre-treatment baseline in FEV_1 AUC and trough FEV_1. Olodaterol showed significant improvements in FEV_1 AUC compared to placebo at week 12 and 24 in all 48-week trials. Trough values were also significantly improved compared to those for placebo. The mean increase in FEV_1 was 0.11 L compared to placebo. The other four trials demonstrated olodaterol's bronchodilatory profile over 24 hours. In 429 patients, the change from pre-treatment baseline in FEV_1 AUC, from 0 to 12 hours, as well as 12- to 24-hours post-dose, was significantly improved in patients taking olodaterol compared to those using placebo.

META-ANALYSES

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists among the various aerosol delivery devices (MDI versus DPI versus nebulizers) used in the management of asthma and COPD exacerbations.[77] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested $beta_2$-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference among devices in any efficacy outcome in any patient group for each of the clinical settings that were investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

A systematic review examined the benefit or detriment on the primary outcome of asthma control with the regular use of long-acting $beta_2$-agonists compared with placebo, in populations in which only some patients were taking inhaled corticosteroids (ICS) and in populations not using ICS.[78] A total of 67 studies (n=42,333) of at least four weeks duration comparing long-acting $beta_2$-agonists (LABAs) given twice daily with placebo were included in the analysis. Salmeterol was studied in 50 trials and

formoterol in 17 trials. Twenty-four studies did not permit the use of ICS, and 40 permitted ICS. In these studies, between 22 and 92% of subjects were taking ICS, with a median of 62%. LABAs were associated with benefits compared to placebo for morning peak expiratory flow (PEF), evening PEF, and FEV_1. Additionally, LABAs were associated with significantly fewer symptoms, less use of rescue medication, and higher quality of life scores. This was true whether patients were taking LABAs as monotherapy or in combination with ICS. Adverse effects such as headache, throat irritation, tremor, and nervousness were more frequent with LABAs.

SUMMARY

Formoterol (Foradil), salmeterol (Serevent), indacaterol (Arcapta Neohaler), and olodaterol (Striverdi Respimat) are long-acting $beta_2$-agonist (LABA) bronchodilators. The main difference between formoterol and salmeterol is that formoterol has an earlier onset of action. Whether this translates to a clinically significant effect is unknown. Indacaterol and olodaterol are not indicated for use in the treatment of asthma nor should it be used in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. Arformoterol (Brovana) and formoterol (Perforomist) are LABAs for nebulization indicated for the twice-daily, long-term maintenance treatment of bronchoconstriction in patients with COPD, which includes chronic bronchitis and emphysema. The nebulized form may prove beneficial for patients who have difficulty synchronizing breath and actuation using the other existing LABAs available as dry powder inhalers (Foradil and Serevent). There are no comparative data to suggest that arformoterol (Brovana) or formoterol (Perforomist) are superior in efficacy or safety to the other agents. Olodaterol is a once-daily administration option. None of the LABAs have demonstrated an impact on delaying the progression of disease or improving survival of patients with COPD.

Consideration should be made to the black box warning which appears in the labeling for all LABAs and may discourage the use of these agents, especially in the African American population.

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